Please add new claims 14 and 15 as follows:

14. (New) The method of claim 1 wherein the polypeptide is an antibody.

15. (New) The method of claim 1 wherein the polypeptide is a monoclonal antibody.

**REMARKS**

After entry of this amendment, claims 1-15 will be pending. Applicants respectfully request reconsideration of the rejections for the reasons below.

Amendments

Claim 1 has been amended to recite that the method is a purification method (see at least page 8, line 15), and to recite that the mixture consists essentially of the monomer and dimer and/or multimer thereof.

Claims 14 and 15 have been added to recite, respectively, that the polypeptide is an antibody (as supported, e.g., in original claim 2) or a monoclonal antibody (as supported, for example, on page 11, lines 15-16).

These claim amendments after Final Rejection present the rejected claims in better form for allowance or consideration on appeal. Hence, entry thereof is respectfully requested.

Rejections under 35 USC §102

Claims 1-2, 5-7, and 9-13 are rejected under 35 USC §102(b) as being anticipated by Yang *et al.*, Journal of Chromatography, A 743 (1996) ("Yang"). The Examiner asserts that the previously presented arguments and Declaration by Steven Cramer, Ph.D., submitted on September 20, 2001, are not commensurate in scope with the claims. According to the Examiner, the instant claims are not drawn to a method of purification, but rather to a method of separation, being thus far more broadly drawn than the Declaration and accompanying arguments would imply. While the Cramer Declaration states that one of skill in the art would not have expected the cation- and anion-exchange techniques known in the art for protein separation to be effective for purifying monomers from solutions consisting of dimers and/or multimers, the Examiner contends that this alleged unexpected result encompasses only purification of monomers from solutions consisting of dimers and/or multimers of the monomer, and thus is not commensurate in scope with claims drawn generally to protein separation from compositions that comprise monomers, dimers and multimers (and thus may contain any other type of material).

As now amended, the claimed invention is directed to a method for purifying polypeptide monomers from a mixture consisting essentially of said

polypeptide monomers and either (i) dimers or multimers of said polypeptide monomers or (ii) both dimers and multimers of said polypeptide monomers. The claimed result is that the monomer is purified from the dimers and/or multimers present in the mixture and the purified monomer has a purity of grcater than 99.5% and the monomer yield is greater than 90%. This amendment applies to all the claims, since claims 2-15 depend on claim 1.

Accompanying this Amendment is a second Declaration from Steven Cramer, Ph.D., explaining that his opinion is based on the amended claim above, which contains the "purification" and "consisting essentially of" wording. This second Declaration clarifies that one of skill in the art would not have expected the ion-exchange techniques known in the art for protein separation to be effective for purifying monomers from solutions consisting essentially of dimers and/or multimers. Hence, the purity and yield results considered unexpected by Dr. Cramer encompass purification of monomers from solutions consisting essentially of dimers and/or multimers of the monomer and are commensurate in scope with the amended claims drawn to protein purification from compositions consisting essentially of monomers and dimers and/or multimers of said monomers.

The wording "consisting essentially of" in claim 1 necessarily excludes from the mixture or solution other unspecified components or ingredients that materially affect the basic and novel characteristics of the invention. See *Ex parte Hoffman*, 12 USPQ 2d1061, 1063 (BPAI 1989); *PPG Indus. Inc. v. Guardian Indus. Corp.*, 48 USPQ 2d 1351, 1353-54 (Fed. Cir. 1998). Hence, this language allows for other ingredients in the mixture to be purified, as is the case with the preparations used in the Examples of this application, but not just any ingredient, so as to distinguish from the bulk, complex mixtures used in Yang (and in the Hahn teaching below).

Dr. Cramer states that his previous Declaration was not drawn to methods of purifying protein monomers from solutions consisting only of multimers and/or dimers of the monomer. His previous arguments apply to the claims of the application as presently amended, which recite a method of separating monomers from mixtures consisting essentially of such monomers along with their dimers and/or multimers. Namely, such mixtures also may contain other components that do not materially affect the fundamental character of the invention. See paragraph 3 of his attached Declaration.

According to Dr. Cramer, the present application discloses the unexpected results of purity and yield when specific reaction conditions are

used for protein purification of commercial solutions as well as anti-IgE antibody, which may contain other proteins, under section B, pages 9-10, besides the multimers and/or dimers of the monomer. He then refers to Figs. 1-6, which represent chromatograms that often show other peaks besides the monomer and dimer. Thus, his conclusions are not drawn specifically to a method of purifying homogeneous mixtures. See paragraph 3.

The case law is clear that to establish inherency, the inherent characteristic must **necessarily** be present in the prior art reference **and** such characteristic would have to have been **recognized** by a person of ordinary skill in the art at the time. Yang does not satisfy both of these.

Addressing the first element of inherency, Dr. Cramer states in paragraph 5 of his second Declaration that at the relevant time of filing the above application (June 1, 1998), the disclosure of Yang would not have conveyed to the relevant skilled practitioner that monomeric proteins can be separated from dimeric and/or multimeric forms thereof contained in mixtures consisting essentially of such monomers, dimers, and multimers and obtained in a yield of such high degree utilizing the ion-exchange technique of Yang. One skilled in the chromatographic field would view Yang in the context in which it is written. Ion-exchange chromatography is a common method for separating proteins, and Yang merely utilizes this technique to carry out what would be expected in the art. Thus, Yang is separating polypeptide monomers from other monomeric forms thereof (such as differently glycosylated or post-translationally different immunoglobulins), or from totally different polypeptide monomers contained in the ascites and sera, or from dimers and/or multimers that may be naturally contained in ascites and sera.

However, Yang does not explicitly disclose separation of such monomers from their own dimers and/or multimers contained in a mixture consisting essentially of these two or three components. The skilled artisan would not have believed as of June 1, 1998 that separation of monomers from their own dimers and/or multimers (in a mixture optionally containing other materials, provided they do not materially change the fundamental and novel character of the process) to produce therapeutically acceptable polypeptides could be accomplished at such high yield and purity by ion-exchange chromatography. Before the filing date, the skilled chromatographic separation scientist was using size-exclusion chromatography for this purpose. Thus, in Dr. Cramer's view, one reasonably skilled in the art would not believe that Yang discloses



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all stated features and elements of the claimed invention. See paragraph 5 of his second Declaration.

In paragraph 6, Dr. Cramer states that the protein loads utilized by Yang in its chromatography would not allow one of reasonable skill in this art to reach the conclusion that purification of monomers from their dimers and/or multimers in a mixture consisting essentially of same would be feasible, much less would necessarily flow from the disclosure of Yang.

As to the second element of inherency, Dr. Cramer states in paragraph 7 that one ordinarily skilled in the art as of June 1998 would not have appreciated or recognized from Yang the feature thought to be inherent, namely, that dimers and multimers could be separated from their own monomers in a mixture that consists essentially of these components, let alone the high yields or purity levels stated. As mentioned above, chromatographic media exist that are designed specifically to separate proteins by size, and these were used by practitioners before June 1998 to achieve the separation of monomers from their dimers and/or multimers in mixtures consisting essentially of such monomers and dimers and/or multimers as claimed. The skilled practitioner would not have recognized that monomers could be separated to the level of purity and yields claimed. Evidence to the contrary is shown by the fact that such ion-exchange purification methods were not used to purify monomers from their dimers and/or multimers in mixtures consisting essentially of these components before the present invention was made, but rather size-exclusion chromatography.

Since Yang lacks the supporting data or description of separation of monomers from their dimers and/or multimers in mixtures consisting essentially thereof, the skilled practitioner, without the teachings disclosed for the first time by the present application, would not have recognized that separation of monomers from their dimers and/or multimers in mixtures consisting essentially of same at such high yields and purity would be possible using the claimed method of purification. See paragraph 7.

In view of the claim amendments and foregoing submissions, applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-2, 5-7, and 9-13 based upon Yang under 35 U.S.C. §102(b).

Claims 1, 2, 5-7, and 9-13 are rejected under 35 USC §102(a) as being anticipated by Hahn *et al.*, Chromatography, 795, 277-287 (1998) ("Hahn"). Just as with Yang, applicants' arguments and the Cramer Declaration regarding Hahn are deemed not commensurate in scope with the claims.



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Applicants first note that claim 1, upon which all other claims depend, is amended as set forth above. In paragraph 8 of his second Declaration, Dr. Cramer refutes the assertion that Hahn teaches purification of immunoglobulins using an identical method to that instantly claimed and that purification in Hahn would thus include elution of the IgG monomers from a mixture (bovine whey) that contains monomers and dimers or multimers. He notes that the claims require that the monomer be separated from its own dimers and/or multimers in mixtures consisting essentially thereof. Hahn teaches separation of various different proteins from each other, all of which are contained in bovine whey, such as IgG from lactoferrin and from lactoperoxidase, referring, e.g., to Table 1 on page 280. There is no evidence in Hahn that any separation has occurred between the monomer and any of its own dimers and/or multimers present in the mixture consisting essentially thereof, as required by the present claims, as opposed to dimers and/or multimers that may naturally be present in bovine whey.

Hahn does not anticipate the instant claims by inherency because the inherent characteristic is not necessarily present in Hahn and would not have been recognized by a skilled artisan at the time.

Dr. Cramer addresses the first element of inherency in paragraph 9 of his second Declaration. He notes that the separation of monomers from dimers and/or multimers thereof in a mixture consisting essentially thereof (the characteristic of the claimed invention deemed to be inherent) is not necessarily or actually achieved by practicing the ion-exchange technique with the protein load mixture used by Hahn to purify immunoglobulins from bovine whey. The ordinarily skilled scientist would not have reasonably concluded from the teachings of Hahn that purification of monomers from their dimers and/or multimers contained in mixtures consisting essentially of these two or three components would be feasible at such high levels of yield and purity in June 1998. Since the inherent characteristic does not necessarily flow from Hahn, it does not anticipate the present claims.

The second element of inherency is also lacking. See paragraph 10 of the new Cramer Declaration. He states that the relevant skilled scientist would not have appreciated or recognized as of June 1998 from Hahn that monomers could be separated from their dimers and/or multimers contained in mixtures consisting essentially of the monomers, dimers, and/or multimers. Since Hahn lacks the requisite disclosure, the skilled scientist would not have recognized that separation of monomers from their dimers and/or



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multimers in mixtures consisting essentially thereof would be possible at such high levels of yield and purity using the claimed purification method.

Since Hahn does not anticipate amended claim 1, upon which all other rejected claims depend, applicants respectfully request reconsideration and withdrawal of the rejection of the claims thereover under 35 USC §102(a).

Rejections under 35 USC §103

Claims 1-2 and 4-13 are rejected under 35 USC §103(a) as being unpatentable over Yang in view of US 4,764,279 ("Tayot"). The Examiner contends that the mixture of Tayot would contain dimers and multimers inherently, and urges that the skilled artisan would reasonably expect that a method useful for purifying proteins that is identical in method steps to the instant method would function identically and thus would perform the specific purification of monomers from dimers and multimers of the monomer, resulting in the same levels of purity as instantly claimed. Further, Tayot was only cited to provide the industrial applicability of purification of albumin, and one could use any art-known purification technique to conduct such purification, including those of Yang.

Claim 1 has been amended as noted above. The law on obviousness is set forth in previously submitted amendments. The deficiencies of Yang with respect to this amended claim are noted above.

The Examiner is directed to paragraph 11 of the second Cramer Declaration stating that the claimed invention would not have been obvious as of June 1998 from the combination of Tayot with Yang. Tayot does not disclose or suggest how one skilled in the art might separate monomers from their own dimers and/or multimers contained in mixtures that consist essentially of such monomers and dimers and/or multimers. Instead, hemoglobin, gamma-globulins, and albumin are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 1 of Tayot), or hemoglobin and albumin are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 10 of Tayot). These protein moieties are not related as monomers and dimers of such monomers and/or multimers of such monomers, as is required in the claimed purification method of the above application. The anion-exchange step described in Tayot is designed such that only albumin binds to the column and the hemoglobin and immunoglobulins flow through the column. The gamma-globulins are separated from the hemoglobin by precipitation in ice-cold ethanol.

Therefore, according to Dr. Cramer (paragraph 11), the purification of IgGs is achieved by a method (precipitation) completely distinct from the presently claimed ion-exchange method (see col. 4, lines 10-54 of Tayot). Tayot further states that the Ig precipitate "...must then be subjected to other purification operations already known so as to prepare immunoglobulins which may be used in human therapeutics" (col. 4, lines 48-51), just as with albumin (compare col. 4, lines 29-31). It is evident that no mention is made of the purification of gammaglobulins or albumin from its dimers and/or multimers. These statements regarding further purification that is required actually teach away from the claims of the above application where no further purification step is used. Hence, one versed in this art, in his opinion, would not be motivated to combine the disclosure of Yang with that of Tayot.

Further, this combination of references did not disclose and would not have suggested the unexpectedly high minimum purity and yield levels claimed by applicants, e.g., greater than 99.5% and greater than 90%, respectively.

Failing to suggest or provide motivation for the invention and to provide a reasonable basis for its success, Yang in combination with Tayot do not meet the standards of obviousness. Specifically, one of ordinary skill in the art would not have had a reasonable expectation that the claimed invention would be successful, and there is no teaching in the references themselves that suggests the combination. Obviousness cannot be predicated on what is unknown. Hence, this rejection of claims 1-2 and 4-13 is in error, and applicants respectfully request that it be withdrawn.

Claims 1-3 and 5-13 are rejected under 35 USC §103(a) as being unpatentable over Yang and Hahn in view of the Oncogene Science catalog 1992, pages 18 and 34. The Examiner contends that the catalog pages are cited to teach the desirability of the purification process, i.e., that purified antibodies are commercially desirable.

The claimed invention would not have been obvious from the Oncogene Science catalog along with Yang and/or Hahn. Steven Cramer, Ph.D. notes in paragraph 12 of his second Declaration that the latter references contain no details or directions to instruct the skilled artisan on how to obtain pure antibodies from impure mixtures consisting essentially of dimers and multimers of the antibody monomers to be purified, for reasons noted above.

As to the Oncogene Science catalog, Dr. Cramer did not set forth in his previous Declaration that the Oncogene Science antibodies are already purified. Rather, he indicated that the antibodies of the catalog are

actually only research-grade material, so that their level of purity has no bearing on the level of purity needed to obtain antibodies suitable for therapeutic needs, as the claimed level of greater than 99.5% reflects. The catalog does not provide the motivation to obtain or desirability of obtaining further purified antibodies, since it is offering for sale less purified antibodies that presumably need no further purification. (They are not antibodies that would be used in therapeutics, which require a high level of purification as set forth in claim 1.) Hence, the catalog would teach away from the invention by indicating no need for further purification of the antibodies. See paragraph 12.

In fact, neither Yang nor Hahn nor the Oncogene Science catalog even acknowledges the existence of dimers and/or multimers of polypeptide monomers, let alone that a purification thereof from the monomers in mixtures that may contain other components can occur so as to obtain highly pure monomeric antibodies. The combined references would not have suggested the claimed invention as herein amended, particularly with the purity and yield results. See paragraph 12.

Hence, reconsideration and withdrawal of the rejection of claims 1-3 and 5-13 under 35 USC §103(a) as being unpatentable over Yang and Hahn in view of the catalog is respectfully requested.

Further evidence of unobviousness

In paragraph 13 of the second Declaration, Dr. Cramer provides further evidence to rebut both obviousness rejections. Specifically, when he first heard about the above-claimed invention, he was surprised that the technique could be applied to purification of monomers from their own dimers and/or multimers (which are all contained in a mixture consisting essentially of such components) at such unexpectedly high minimum purity and yield levels obtained as claimed, i.e., greater than 99.5% and greater than 90%, respectively. Size-exclusion chromatography was the gold standard at the time for distinguishing between these very similar protein species. His colleagues and he working in the separation arts would not have expected from Yang combined with Tayot or from Yang and Hahn in combination with the selected catalog pages that such a high yield and purity could be achieved.

There is thus nothing in the collection of references that would have motivated the skilled artisan to purify the polypeptide monomers from their dimers and multimers to the claimed purity and yield levels using the claimed method at the priority date.

Summary

Steven Cramer, Ph.D. summarizes the evidence supporting patentability of the claimed invention in paragraph 14 of his second Declaration. He states that the above citations alone or in combination merely disclose that proteins can be purified to some degree using ion-exchange chromatography. In particular, the disclosures clearly show separation of IgG from BSA or IgG partially separated from whey, serum, or ascites proteins, etc. None of the cited references even mentions the existence of dimers and/or multimers of polypeptide monomers.

Nowhere do these references, alone or in combination, mention or suggest the purification of monomers from their dimers/multimers in mixtures consisting essentially of the monomers and dimers and/or multimers using ion-exchange chromatography as claimed, much less with the claimed yield and purity results. Such results would not have necessarily followed from practicing the teachings of these references, due to the nature of the mixtures being loaded on the column in these references. The skilled practitioner would not have appreciated or expected from these teachings that such could be done. See paragraph 14.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

For the Examiner's convenience, a clean copy of the currently pending claims is attached hereto.

It is believed that the now-pending claims are in condition for allowance based on the foregoing submissions. If the Examiner has any questions regarding this response, she is invited to call the undersigned.

Respectfully submitted,
GENENTECH, INC.

Date: March 29, 2002

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Serial No. 09/320,100

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims:**

Claim 1 has been amended as follows, with underlining and bold indicating added text and brackets and strikeout indicating deleted text:

1. (Four-times amended) A method for [~~separating~~] **purifying** polypeptide monomers from a mixture [~~comprising~~] **consisting essentially of** said polypeptide monomers, and dimers or multimers of said polypeptide monomers or both dimers and multimers of said polypeptide monomers, wherein the method consists essentially of applying the mixture to a cation-exchange or anion-exchange chromatography resin in a buffer, wherein if the resin is cation-exchange, the pH of the buffer is about 4-7, and wherein if the resin is anion-exchange, the pH of the buffer is about 6-9, and eluting the mixture at a gradient of about 0-1 M of an elution salt, wherein the monomer is [~~separated~~] **purified** from the dimers or multimers or both present in the mixture, and wherein the [~~separated~~] **purified** monomer has a purity of greater than 99.5% and the monomer yield is greater than 90%.

Claims 14 and 15 have been added as follows:

--14. (New) The method of claim 1 wherein the polypeptide is an antibody.--

--15. (New) The method of claim 1 wherein the polypeptide is a monoclonal antibody.--



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